Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 22-24, 28-32, 35 and 37-43 are pending in the application. The amendment to the claims is believed to introduce no new matter, and its entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

I. Miscellaneous

Applicants thank Examiner Beckerleg for the courtesy of the telephone discussion of May 5, 2001. During that discussion, the undersigned pointed out that given the circumstances it was not believed that a Final First Action should have been mailed. This conclusion was based on the fact that an Advisory Action was issued on March 16, 2000 indicating that the "proposed amendments would not be entered because: they raise new issues that would require further consideration and/or research." Thus, applicants should be entitled to full consideration of their previously filed amendment which precludes issuance of the finality. At the conclusion of the discussion, the Examiner agreed to remove the finality of the first office action.

Applicants note that the examiner has acknowledged "applicant's previously stated intent to correct the defects in the declaration" when allowable subject matter has been indicated.

II. Amendment to the Claims

Applicants have amended claims 22 and 28 to recite "an aerosolized adenoviral vector" and also recited "aerosol delivery" and "adenoviral vector" in claim 37. Support for theses amendments can be found in the specification at *inter alia*, Example 3. Additionally, Applicants have added new claims 42 and 43 which are also supported at least by Example 3.

III. Rejection of Claims 22-41 Under 35 U.S.C. § 112, First Paragraph

In the Office Action mailed January 17, 2000, the Examiner rejected claims 22-41 under 35 U.S.C. § 112, first paragraph because the arguments and declaration of Dr. Janssens had not been found persuasive in overcoming the grounds of rejection for reasons or record as discussed in detail below. Applicants respectfully traverse this rejection, incorporate by reference herein, reiterate and expand upon the after final reply filed December 27, 1999 and the Preliminary Amendment of September 7, 2000.

Specifically, at page 3 of the office action the Examiner stated:

> In view of applicant's arguments and the declaratory statements of Stefan Janssens, the scope of enablement has been modified. The modifications are underlined below for clarity. The specification, while being enabling for a method of inducing vasodilation in a mammal comprising: introducing into the lungs of a mammalian patient in need of pulmonary vasodilation an aerosolized adenoviral vector comprising a wild type nitric oxide synthase gene operably linked to a strong viral promoter, wherein the introduction of said gene into the lungs of said patient results in pulmonary vasodilation that does not significantly affect systemic blood pressure or cardiac index, and a method of treating hypoxic pulmonary hypertension in mammals comprising introducing into the lungs of said mammal in need of pulmonary vasodilation an aerosolized adenoviral vector comprising a wild type nitric oxide synthase gene operably linked to a strong viral promoter, wherein the introduction of said gene into the lungs of said mammal results in pulmonary vasodilation that does not significantly affect systemic blood pressure or cardiac index, does not reasonably provide enablement for a

method of treating any and all forms of primary or secondary hypertension in all mammals comprising introducing by any route of delivery, any vector encoding any nitric oxide synthase gene under the control of any promoter.

Applicants disagree with the Examiner's arguments as set forth above. Solely, in an effort to expedite prosecution and without acquiescing in the propriety of any aspect of the rejection, however, Applicants have agreed to amend the claims to refer to an "aerosolized adenoviral" vector. The amendment to the claims addresses two of the Examiner's concerns.

While the Examiner has initially requested limitation of the claims to a "strong viral promoter," during the telephone discussion of May 5, 2001 the Examiner indicated that the use of the recitation "viral promoter" without "strong" should be sufficient to replace "an expression control element." Regardless, Applicants disagree with the necessity of replacing the recitation "an expression control element" with a "viral promoter" because sufficient guidance for using "expression control elements" was provided in the specification. Additionally, one of skill in the art would also be aware of "expression control elements" from the art that could have been used in the invention.

Several control elements that could be used in the claimed invention were known prior to July 17, 1996 such as for example, Rust *et al., Am. J. Respir. Cell Mol. Biol. 14*:121-130, 1996 (the surfactant D promoter); Solway *et al., J. Biol. Chem. 270*:13460-13469, 1995 (the SM22 alpha promoter); Lee *et al., J. Biol. Chem 25*:10446-10450, 1990 (the endothelin-1 promoter) and Zhang *et al., J. Biol. Chem. 270*:15320-15326, 1995 (the ceNOS promoter).

Furthermore, other than suggesting the use of a "viral promoter" to replace "expression control elements", the Examiner failed to provide any reason whatsoever why "expression control elements" are not enabled. Additionally, the Examiner failed to directly

address any of the Applicants arguments submitted in the After Final Reply filed December 27, 1999 or the Preliminary Amendment.

For example, the Examiner has failed to address Paragraph 16 of Dr. Janssens declaration that recites as follows:

> 16. Several expression control elements for the expression of transferred genes in lung tissue, other than those disclosed in the specification, were known in the art as of our priority date. For example, it was known that the long terminal repeat of the Rous sarcoma virus is active in a broad range of cells. Sambrook *et al.*, *Molecular Cloning: A Laboratory Manual*, 2nd ed. § 16.6 (Cold Spring Harbor Laboratory Press 1989)(submitted previously as Document No. AT26). It was also known that the adeno-associated virus p_5 promoter and the adeno-associated virus ITR sequence each function as a promoter and can induce expression of a transgene in a lung epithelial cell line, and that the endothelin-1 promoter and the eNOS promoter can direct expression in endothelial cells. Flotte, T.R., *et al.*, *J. Biol. Chem. 268:*3781-90 (1993); (submitted previously as Document No. AS20); Lee *et al.*, *J. Biol. Chem. 265:*10446-50 (1990); Zhang, *et al.*, *J. Biol. Chem. 270:*15320-26 (1995) (submitted herewith as Document Nos. AT34 and AR43). Moreover, it was also know that the surfactant D promoter can direct expression in type II alveolar lining cells, and that the promoter sequences from the human surfactant protein-C (SP-C) can direct expression of a transgene to alveolar type II cells and distal bronchiolar epithelial cells. Rust *et al.*, *Am. J. Respir. Cell. Mol. Biol. 14:*121-30 (1996)(submitted herewith as Document No. AT38); Huffman, J.A. *et al.*, *J. Clin. Invest.* 97(3):649-655 (1996)(submitted previously as Document No. AT21). Finally, it was also known that the SM 22 alpha promoter can be used to direct expression in smooth muscle cells. Solway *et al.*, *J. Biol. Chem. 270:*13460-69 (1995) (submitted herewith as Document No. AR41). In view of the information disclosed in the specification, and known in the art as of our priority date, it is my understanding and belief that the selection of expression control elements for the expression of a transgene in lung tissue, would not require undue experimentation by one of skill in the art.

Additionally, in the specification Applicants taught use of additional expression control elements such as the SV40 polyadenylation signal sequence that may be used in the claimed invention. (*See* the specification at page 15, lines 10-11 and page 18, line 19. The

examiner failed to this. Thus, more than merely promoters are provided to one of skill in the art.

Thus, the Examiner has failed to address Applicants' previous arguments, has failed to address Applicants' declaratory evidence and has failed to elaborate any reason whatsoever, why the recitation "expression control element" is not enabled for the claim. If the Examiner continues to maintain this aspect of the rejection, she is respectfully requested to address the arguments previously raised in the Replies filed on December 27, 1999 and September 7, 2000, particularly as they related to the issues raised in Dr. Janssens' declaration.

The Examiner elaborated on the issue of the nitric oxide synthase gene as follows beginning at the bottom of page 3 of the Office action.

> In regards to identifying and using NOS mutants in the instant invention, the applicant's representative and the declaratory statements of Stefan Janssens argue that the prior art provides sufficient guidance for making mutants of NOS which retain wild type functionality. In support of this argument, the applicant has submitted a number of prior art references. These references provide information about specific residues or regions in various species and isoforms of NOS which affect various aspects of NOS activity. The applicant states that with this body of information, the skilled artisan would be advised as to which residues and regions to avoid mutating and as such undue experimentation would not be required to make NOS mutants with wild type activity. However, the prior art references serve to demonstrate that the NOS molecules are complex and that numerous residues are important to functionality. Further, as discussed in the previous office action, even mutating residues which are not critical for a particular functionality can have profound effects on protein folding, half-life, and pH and temperature sensitivity. The specification does not disclose a single mutant NOS molecule which retains wild type NOS activity Further, the two ceNOS mutants reported by Chen *et al.* (document AT30) and alleged by the applicant to represent NOS mutants suitable for use in the instant invention have significantly reduced enzymatic activity compared to wild type NOS (Chen *et al.*, page 25064, Figure 2). It is also noted that the Chen *et al.* paper does not report on the half-life or stability of the mutated NOS.

It is irrelevant whether the specification discloses a single NOS mutant or more than one mutant if such information would have been know to those of skill in the art. Applicants have clearly set forth at least one of the components of the invention, i.e. the use of a wild-type NOS gene. Additional NOS genes, however, were known in the art prior to the filing date as evidenced by Chen *et al., J. Biol Chem. 269*:25062-25066, 1995. It is clearly stated in the abstract of Chen that mutants at position 441 and 235 "displayed considerable NOS activity." Thus, sufficient information was available in this publication to enable one to prepare NOS mutants that could be used as transgenes having enzymatic activity sufficient for use in the claimed invention. The Examiner has provided no rebuttal of this presumption.

In discussing Chen, the Examiner set forth a number of concerns as follows. First, the two ceNOS mutants reported by Chen *et al.* have significantly reduced enzymatic activity compared to wild type NOS (Chen *et al.*, page 25064, Figure 2). This statement appears to be irrelevant to the rejection and also incorrect both in view of Figure 2 as well as the authors' own statements. As pointed out above the mutants 235 and 441 were considered by the publication's authors to have retained "considerable" activity. This is supported in Figure 2 where the mutants appear to have between approximately 50-75% of the wild-type activity depending upon the conditions used to measure it. There is no reason to believe that this level of activity is insufficient for the successful use of such mutants in the claimed invention. If the Examiner is able to provide evidence to support her belief that such mutants will *not* work in the claimed invention, she is respectfully requested to do so in the next office action. In the absence of such evidence, however, Chen should be considered to provide support for enablement of the claimed invention.

Second, the Examiner is concerned that the Chen *et al.* paper does not report on the half-life or stability of the mutated NOS. Neither of these characteristics are dispositive to the rejection provided that the mutants can be used in the invention. Regardless of whether the ceNOS mutants have reduced activity or different half-lives the Examiner has presented no reason whatsoever to believe that they could *not* be used in the invention as Applicants have argued. Merely having reduced activity does not mean *no* activity or that the mutants have no use in the invention. As long as the gene encodes a protein having a reasonable level of enzymatic activity as ascertained by one of skill in the art, the mutant should still be useful in the invention. Further, one of skill in the art could minimize the experimentation by eliminating those described mutants with little or no activity. Thus, the arguments presented by the Examiner with respect of half-life or stability clearly fail to establish that undue experimentation would be required to practice the claimed invention using mutant genes known in the art. This is particularly true in view of Dr. Janssens' declaration and assertion to the contrary (See Paragraph 10 of the declaration.).

Beginning in Dr. Janssens declaration at page 3 and continuing to page 5, a large amount of information was presented concerning the use of NOS mutants in the invention. With the exception of Chen *et al.*, (document AT30), the Examiner has not specifically addressed any of the publications cited or arguments that the Applicants made. Rather, several generalized statements are made in an attempt to minimize the publications' support for Applicants arguments. Contrary to this, Applicants have provided specific information from a large number of the publications to support their position.

The Examiner's arguments can be summarized as follows:

- NOS molecules are complex and numerous residues are important to functionality.
- Mutating residues which are not critical for a particular functionality can have profound effects on protein folding, half-life, pH and temperature sensitivity.
- The specification fails to disclose a single NOS mutant that retains wild type NOS activity.
- The ceNOS mutant reported by Chen have significantly reduced enzymatic activity compared to wild type NOS.
- Chen fails to report on the half-life or stability of the mutated NOS.

Merely because NOS molecules are complex or specific residues related to function are not indicated in the specification or various characteristics such as temperature sensitivity of mutant molecules are unknown, this does not result in non-enablement. It is speculation on the Examiner's part that one of skill in the art need have this information in order to practice the claimed. One need merely know how to make and use the claimed invention. Lack of knowledge of any or even all of the characteristics set forth by the Examiner would not preclude one of skill in the art from making and using a NOS mutant to practice the invention.

As indicated in Dr. Janssens' declaration at paragraphs 7-9, the art was replete with both positive and negative information relating to NOS mutants. Thus, one of skill in the art availing themselves to the specification and what was known in the art at the time of filing would be able to make a NOS mutant for use in the invention without undue experimentation. The Examiner is respectfully reminded that Applicants are not attempting

to claim NOS mutants *per se*. Rather, a NOS mutant is no more than a component that may be used in the invention.

In the specification beginning at page 12 and continuing to page14 Applicants have provided guidance to preparation or obtaining possible mutant for use in the invention. This includes, but is not limited to:

- Use of nitric oxide synthase isoforms such as iNOS or nNOS.
- Deletion of contiguous amino acids ranging from 1-30 residues and preferably 1-10 residues. Additionally information is provided concerning areas where mutations should not be made.
- Specific substitutions that may be made (See Table 1).

All of this information would permit one of ordinary skill in the art to practice the claim invention without undue experimentation.

At page 5, in an attempt to support the rejection, the Examiner stated as follows:

> a specification need not disclose what is well known in the art. See, e.g., *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. Genentech Inc. v. Novo Nordisk A/S, 42 USPQ2d 1005 (CAFC 1997)

The Examiner's attention is respectfully drawn to the recitation"however, when there is *no* disclosure of *any* specific starting material or any of the conditions under which a process can be carried out, undue experimentation is required." (Emphasis added). This is not the situation that applies to Applicants' application. Clearly, as indicated in the earlier paragraphs, Applicants have provided specific starting materials in both the working examples and elsewhere in the specification for the use of NOS mutants. Additionally, conditions for practicing the invention were also provided. Therefore, this aspect of the rejection is overcome and should be withdrawn.

In the Office Action, beginning at the last paragraph of page 5 and continuing to page 8, the Examiner provides arguments concerning why the invention is allegedly not enabled for use of any vector or manner of vector administration. Applicants respectfully disagree with the Examiner's arguments, however, solely in an effort to expedite prosecution Applicants have amended the claims to recite "aerosolized adenoviral vector." Therefore, this aspect of the rejection is now moot.

Beginning at page 8, last paragraph of the Office Action, the Examiner attempts to rebut Applicants' previous arguments concerning the reason why the application is enabled for treatment of pulmonary hypertension. In this regard, the Examiner states:

> The applicant argues that the rat model in an excepted [sic] model for pulmonary hypertension in humans. Applicant's arguments have been accepted in part. As stated above, the scope of enablement has been modified to recite that the specification is enabling for a method of treating hypoxic pulmonary hypertension in mammals comprising introducing into the lungs of said mammal in need of pulmonary vasodilation an aerosolized adenoviral vector comprising a wild type nitric oxide synthase gene operably linked to a strong viral promoter, wherein the introduction of said gene into the lungs of said mammal results in pulmonary vasodilation that does not significantly affect systemic blood pressure or cardiac index. However, the specification still fails to provide enablement for the treatment of any forms of pulmonary hypertension. As discussed in detail in previous office actions, primary

> pulmonary hypertension is a rare and difficult to diagnose disorder. According to Giuseppe Pietra, plexogenic pulmonary arteriopathy (PPA), characterized variably by concentric laminar intimal fibrosis, plexiform lesions, and necrotizing arteritis, is the most common form of arteriopathy in primary pulmonary hypertension (Pietra (1994) Chest, Vol. 105 (2 supp.), page 3S-4S). Secondary pulmonary hypertension, on the other hand, occurs as a result of an underlying defect or condition such as cardiac septal defects, and cirrhosis. While neointimal formation as a result of smooth muscle cell migration and proliferation resulting in a physical narrowing of the artery is characteristic of most forms of pulmonary hypertension, both primary and secondary, the diseases themselves are extremely complex and characterized by numerous symptoms. The specification defines treatment as including prophylaxis, amelioration, or cure (specification, page 10, lines 10-13). Thus the term treatment is broad and encompasses a wide variety of effects on the disease. Of these, the specification only provides enablement for inducing pulmonary vasodilation without significantly affecting systemic blood pressure or cardiac output. Based on the complex nature of hypertensive diseases, the known activities of NOS, the applicant's working examples, and the well known unpredictability of treating primary and secondary hypertension, the skilled artisan would not consider the applicant demonstration of increased vasodilation as evidence that the administration of NOS to the vasculature of patients would either prevent or cure the myriad of symptoms associated with hypertensive conditions.

Applicants disagree with the Examiners' conclusion regarding the scope of enablement for the claims.

While the Examiner refers to the model used by Applicants, the Examiner has failed to provide any reason whatsoever why the model is not appropriate for pulmonary hypertension other than hypoxic pulmonary hypertension. Nothing has been provided from the literature that rebuts Applicants assertions concerning the model. The Examiner has merely elaborated on the pathology or etiology of primary or secondary hypertension. This is not the issue. The issue is whether the Examiner can provide substantiation from the art that the hypoxic rat model is not appropriate for studying pulmonary hypertension in general. No such information has been provided.

Applicants have asserted that they have used an appropriate and accepted model to establish the effects of treatment on hypertension. Further, Applicants have set forth a specific rebuttal of the publication used by the Examiner and the Examiner has failed to address this argument in maintaining the rejection. For the Examiner's convenience, Applicants again provide the arguments made in the reply filed December 27, 1999 and respectfully request that the Examiner specifically address the following issues previously raised by Applicants.

> The Examiner's last contention is that the claims are not enabled for the treatment of any and all forms of pulmonary hypertension in any and all mammals. In support of this contention, the Examiner argues that the rat model, used in the examples in the application, is not a good model for pulmonary hypertension in humans, therefore, the treatment of this disease is not enabled for humans. The Examiner relies on a statement in Heath that alleges that the rat is not a good model for this disease in humans, because the rat does not undergo the migration of smooth muscle cells into the intima of blood vessels, which occurs in the disease in humans. Heath, D., *Eur. Respir. Rev. 3:* 555-58 (1993). Further, the Examiner found Applicants' reliance on Roberts *et al.,Circ. Res. 76:*215-222 (1995), unpersuasive because the rat model was used for the experiment reported in that paper.
>
> At most, the statement in Heath indicates that results from tests showing the effect of nitric oxide on vascular structural changes in rats may not be used to draw conclusion regarding its effect on smooth muscle cell migration in humans. However, Rabinovitch et al., contradicts this statement in Heath, by teaching that one of three abnormal features found in arterial circulation in the lungs of hypoxic rats is the "extension of muscle [i.e., migration of muscle cells] into smaller and more peripheral arteries than normal." Rabinovitch, M., *et al., Am. J. Physiol. 236:*H818-27, at 822, col. 1, lines 29-32 (1979)(Attached as Exhibit S); *see also* Reid, L and Meyrick, B., *Excerpta Medica, Metabolic Activities of the Lung, Ciba Found. Symp. 78:*37-60, at 44, para. 4 to 45, para. 1 (1980)(Attached as Exhibit T); Roberts, J.D., *et al. Circ. Res. 76:* 215-222, at 215, col. 2, lines 22-26 (1995) (Attached as Exhibit U). Further, Rabinovitch *et al.*, states that the degree of abnormal extension (i.e., migration) of muscle into peripheral arteries "proved to convey the totality of morphological information: when abnormal extension of muscle is taken into account, neither increased wall thickness of the muscular arteries nor increased ratio of alveoli to arteries [the other two morphological changes reported to occur in the arteries of hypoxic rats] correlates with pulmonary artery pressure . . . . These two features are informative only as surrogates for extension of muscle." *Id.* at H824, col. 1,

lines 1-12. In fact, nitric oxide inhalation was reported by Roberts *et al.*, to reduce the extension of smooth muscle into peripheral lung arteries. Roberts, J.D., *et al. Circ. Res. 76:* 215-222, at 215, col. 2, lines 22-26 (1995). These papers counter the assertion in Heath that the rat is not an appropriate model for pulmonary hypertension in humans.

In addition, the rat exhibits other structural changes in the pulmonary vasculature, including smooth muscle cell proliferation, differentiation and hypertrophy, that occur in pulmonary hypertension in humans. *See* Janssens, *et al., J. Appl. Physiol.* 77(3):1101-1107 (1994) (Attached as Exhibit V); Roberts, J.D., *et al. Circ. Res. 76:* 215-222 (1995). These shared structural changes further support the use of the rat as a model for pulmonary hypertension in humans. Moreover, Applicants' own post-filing experiments suggest that nitric oxide inhibits at least some of these structural changes to pulmonary vasculature. This data shows that the transfer of a NOS gene to the lung suppressed the muscular hypertrophy that accompanies hypoxia in rats.

Finally, the recitation of the word "treating" in the claims relating to the treatment of pulmonary hypertension does not require that the disease be cured. The specification defines "treating" on page 10, lines 10 through 13, as including "the administration of therapeutic compositions of the invention to a subject for purposes which may include prophylaxis, amelioration, prevention, or cure of a medical disorder, such as pulmonary hypertension." Thus, even if the administration of nitric oxide is never shown to prevent or alter the pathological structural changes of pulmonary hypertension in humans, the fact that it ameliorates the disease in humans is sufficient to enable these claims for the treatment of humans. Therefore, Applicants maintain that the claims drawn to methods of treating pulmonary hypertension are enabled.

Applicants wish to reiterate that the hypoxic rodent model was used because its pathophysiology shares several essential components of primary and secondary pulmonary hypertension in human patients, including pulmonary vasoconstriction and pulmonary vascular remodeling. Patholophysiological alterations in the pulmonary circulation share common characteristics in rodents and men and drugs which are pulmonary vasodilators in rat have been found to be vasodilators in patients. Thus, there is no reason to believe that Applicants have failed to enable the full scope of the claim by using the hypoxic rodent model. While the Examiner may point to discussion of the pathology of the rat model, this fails to support an argument that the model is not representative of pulmonary hypertension,

particularly in light of the Applicants' declaration to the contrary. If the Examiner maintains the position concerning the rat model, she is respectfully requested to provide a publication indicating that such a model cannot be representative of anything other than hypoxic hypertension. In the absence of such information, the Examiner must accept Applicants averments.

The Examiner completed this aspect of the rejection referring to "the well known unpredictability of treating primary and secondary hypertension" and that "the skilled artisan would not consider the Applicants' demonstration of increased vasodilation as evidence that the administration of NOS to the vasculature of patients would either prevent or cure the myriad of symptoms associated with hypertensive conditions." This appears to be mere speculation on the Examiner's part and the Examiner is respectfully requested to support the arguments by reference to citations in the art concerning the so-called "well-known unpredictability" of treating pulmonary hypertensive patients and that one of skill in the art would fail to accept Applicants' evidence. If Applicants claim to have provided evidence to support enablement such as that in Paragraphs 24-27 of Dr. Janssens' declaration, then the Examiner must accept this at face value or otherwise rebut it with objective evidence to the contrary, not merely an assertion that the evidence does not support Applicants' position.

Applicants traverse the assertion that there is "well known unpredictability of treating primary and secondary hypertension." (Office Action at page 9, 3 lines from the bottom). Applicants further request the examiner to provide a reference in support of this specific position as required in MPEP § 2144.03. If the Examiner cannot provide an appropriate reference, Applicants assume that the unpredictability of treating hypertension

is personal knowledge of the Examiner and request an Examiner's affidavit as required by the same section of the MPEP.

> When a rejection is based on facts within the personal knowledge of the examiner, the data should be stated as specifically as possible, and the facts must be supported when called for by the applicant, by an affidavit from the examiner.

MPEP § 2144.04 (Page 2100-103, left-hand column). In the absence of either appropriate citation from the art or an Examiner's affidavit there is no basis for an assertion of unpredictability. Based on the lack of unpredictability as well as other aspects of the Applicants' rebuttal, there is no basis for arguing undue experimentation would be required to practice the invention or that one of skill in the art would not believe that Applicants' invention would treat pulmonary hypertension. Therefore, the rejection cannot stand.

Based on all of the above, this rejection is overcome and should be withdrawn.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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SKGF Rev. 2/13/01

Version with markings to show changes made

22. (Amended) A method of inducing pulmonary vasodilation comprising:

introducing [a] an aerosolized adenoviral vector comprising a nitric oxide synthase gene operably linked to an expression control element into the lungs of a mammal in need of pulmonary vasodilation;

wherein the introduction of said vector into the lungs of said mammal results in pulmonary vasodilation that does not significantly affect systemic blood pressure or cardiac index.

28. (Amended) A method of treating pulmonary hypertension comprising:

introducing [a] an aerosolized adenoviral vector comprising nitric oxide synthase gene operably linked to an expression control element into the lungs of a mammal in need of treatment for pulmonary hypertension;

wherein the introduction of said vector into the lungs of said mammal results in pulmonary vasoldilation that does not significantly affect systemic blood pressure or cardiac index.

35. (Amended) The method of treating pulmonary hypertension as claimed in claim [34] 28 wherein said adenovirus vector is AdCMVceNOS.

37. (Amended) A pharmaceutical composition suitable for aerosol delivery comprising a nucleic acid encoding a nitric oxide synthase gene operably linked to [an expression control element, and a pharmaceutically acceptable carrier vehicle; wherein said expression control element selectively expresses said nucleic acid encoding a nitric oxide synthase in pulmonary tissue.